

Stainless steel canister for propellant-driven metering aerosols

Related Applications

5 This application is a continuation of U.S. Application Serial Number 09/580,246, filed May 26, 2000, which claims benefit of U.S. Provisional Application Serial No. 60/167,772, filed on November 29, 1999, both of which are herein incorporated by reference in their entirety.

10 **Field of the Invention**

The present invention relates to corrosion-resistant stainless steel canisters for propellant gas-containing aerosol formulations for use in propellant gas-operated inhalers.

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Background of the Invention

In propellant-driven inhalers, the active substances are stored together with the propellant in cartridge-like canisters. These canisters generally consist of an aluminium container sealed with an aluminium valve cup in which a valve is embedded. A canister of this kind can then be placed in the inhaler in the manner of a cartridge and is either left there permanently or replaced with a new cartridge after use. Since chlorofluorocarbons (CFCs) were proscribed on the grounds of their ozone-destroying properties at the Rio de Janeiro Conference at the beginning of the 90s, the use of fluorohydrocarbons (FHC) is promoted as an alternative for use in propellant-driven inhalers. The most promising example to date are TG 134a (1,1,1,2-tetrafluoroethane) and TG 227 (1,1, 1,2,3,3,3-heptafluoropropane). Accordingly, existing systems of delivery for treatments by inhalation have had to be converted to CFC-free propellants and new delivery systems and active substance formulations have had to be developed.

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Surprisingly, it has been found that aluminium canisters are not always resistant to drug formulations containing fluorohydrocarbons as propellants but have a high risk of corrosion depending on the composition of the formulations. This is particularly true of formulations which contain electrolytes and/or free ions, particularly free halides.

5 In these cases, the aluminium is attacked, which means that aluminium cannot be used as a casing material for the canisters. Similar instabilities in the aluminium canisters have been observed when fluorohydrocarbons are used as propellants if the formulations contain acid or basic components, e.g. in the form of the active substances, the additives, in the form of stabilisers, surfactants, flavour enhancers,
10 antioxidants, etc.

Brief Description of the Drawings

Fig. 1 shows a canister consisting of container (2), valve cup (8) and the valve (9) in
15 cross-section.

Fig. 2 shows another embodiment of the valve cup (8) and the valve (9) in cross-section.

Detailed Description of the Invention

20 One of the tasks of the present invention is to provide a canister for propellant-driven inhalers which is corrosion-resistant in the presence of active substance formulations for inhalation therapy containing a fluorohydrocarbon as propellant, which has sufficient compressive and breaking strength to withstand processing and use, which
25 ensures the quality of the formulations stored therein and overcomes the other disadvantages known from the prior art.

The invention solves this problem by providing a canister for propellant-driven inhalers which consists predominantly of an alloy which is corrosion-resistant in the
30 presence of drug formulations containing fluorohydrocarbons. The components of this alloy contain chromium (Cr), nickel (Ni), molybdenum (Mo), iron (Fe) and carbon (C). In another embodiment the alloy additionally contains copper (Cu), manganese

(Mn) and silicon (Si). The canister according to the invention consists of a container (2) and a valve cup (8) with valve (9). The container preferably consists of one of the alloys described below. The invention therefore also relates to a container of this kind.

- 5 The invention further relates to the use of a container or canister of this kind consisting of a container (2) and a valve cup (8) with valve (9) in propellant-operated metering aerosols (inhalers) and a process for producing them.

The invention is hereinafter explained more fully with reference to Figures 1 and 2.

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Fig. 1 shows the canister consisting of container (2), valve cup (8) and the valve (9) in cross-section.

Fig. 2 shows another embodiment of the valve cup (8) and the valve (9) in cross-section.

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Figure 1 shows the canister (1) according to the invention in cross-section. The canister (1) consists of a container (2) for holding the pharmaceutical formulation and a valve cup (8) with valve (9). The shape and dimensions of the canister correspond to those of the aluminium canisters known from the prior art.

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The container (2) according to the invention is made of an alloy comprising the following elements in the amounts indicated:

Iron (Fe) of 40,0 – 53,0%,

25 Nickel (Ni) of 23,0 – 28,0%,

Chromium (Cr) of 19,0 – 23,0%,

Molybdenum (Mo) of 4,0 – 5,0%,

Manganese (Mn) of 0,0 – 2,0%,

Copper (Cu) of 1,0 - 2,0%,

30 Silicon (Si) 0,0 - 1,0%,

Phosphorus (P) 0,0 - 0,045%,

Sulfur (S) 0,0 - 0,035% and

Carbon (C) 0,0 - 0,020%;
with the proviso that the alloy does not contain aluminum.

In one embodiment, this alloy further comprises nitrogen of about 0.0 to about 0.15%,
5 for example of about 0.04 to about 0.15%.

This alloy is one according to the material number 1.4539 of the steel-iron-list of the
association of the German iron-works-worker (in German language:
Werkstoffnummer der Stahl-Eisen-Liste des Vereins deutscher Eisenhüttenleute).

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A preferred alloy of this type has the following composition:

Chromium (Cr) 19,0 - 21,0%,

Nickel (Ni) 24,0 – 26,0%,

Molybdenum (Mo) 4,0 – 5,0%,

15 Copper (Cu) 1,0 – 2,0%,

Manganese (Mn) up to 2,0%,

Silicon (Si) up to 0,5% und

Carbon (C) up to 0,02%, whereby the remainder consists essentially of iron.

20 For a nearly identical alternative alloy the content of Molybdenum is limited to 4,5-
5,0%.

In an alternative embodiment the container (2) according to the invention consists of
an alloy according to the material number 1.4404 of the steel-iron-list of the

25 association of the German iron-works-worker (in German language:

Werkstoffnummer der Stahl-Eisen-Liste des Vereins deutscher
Eisenhüttenleute)consisting of

Iron (Fe) 60,0 – 72,0%,

Nickel (Ni) 9,0 – 13,0%,

30 Chromium (Cr)17,0 – 21,0%,

Molybdenum (Mo) 2,0 – 3,0%,

Manganese (Mn)0,0 – 1,5%,

Silicon (Si) 0,0 - 1,5%,
Phosphorus (P) 0,0 - 0,04%,
Sulfur (S) 0,0 - 0,04% und
Carbon (C) 0 - 0,03%.

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Another embodiment of the canister (2) consists of an alloy consisting of:

Chromium (Cr) 16,5 - 18,5 %,
Nickel (Ni) 11,0 - 14,0%,
Molybdenum (Mo) 2,0 - 2,5%,

10 Carbon (C) up to 0,03% and iron as the remaining component.

The alloys mentioned above are such that they are corrosion-resistant to various liquefied fluorohydrocarbons such as TG 134a (1,1,1,2-tetrafluoroethane) and TG 227 (1,1,1,2,3,3,3-heptafluoropropane). These include propellant gas formulations having
15 active substances suitable for inhalation therapy, surfactants, cosolvents, stabilisers, complexing agents, flavour correctors, antioxidants, salts, acids, bases or electrolytes, such as hydroxide ions, cyanide ions and/or halide anions such as fluoride, chloride, bromide or iodide.

20 The container (2) is formed from a casing made of one of the alloys described above. The container (2) has four different zones: the flat or concave, inwardly domed base (3), a cylindrical portion (4) which merges into the tapering neck (5) in its upper third and finally ends in the bead (6) which encircles the opening (7) of the container.

25 The wall thickness of the container (2) is between 0.1 and 0.5 mm in a preferred embodiment, preferably between 0.15 and 0.35 mm, most preferably about 0.19 to 3.0 mm.

In a preferred embodiment the container (2) will withstand a bursting pressure of more
30 than 30000 hPa, preferably more than 100000 hPa, most preferably more than 200000 hPa. The weight of the container (2) is 5-15 g in a preferred embodiment, 7-10 g in another and 7.9 - 8.7g in yet another. In an equally preferred embodiment the

container (2) has a volume of 5 to 50 ml. Other containers have a volume of 10 to 20 ml whilst still others have volumes of about 15 - 18 ml.

5 In the sealed state the container (2) is tightly sealed by means of the valve cup (8) after being filled with the pharmaceutical formulation and the propellant.

In another embodiment the valve cup (8) also consists of corrosion-resistant material. Preferably this is one of the alloys described above for the containers and/or a plastics material of suitable pharmaceutical quality.

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In another embodiment the valve cup (8) consists of aluminium. In this case the seal (10) and/or the valve (9) are constructed so that the valve cup (8) itself cannot come into contact with the liquid inside the container.

15 A preferred embodiment of the valve cup (8) is as described in GB 2324121, to which reference is hereby made.

In the closed state of the canister, the valve cup (8) is crimped around the container (2) at its bead (6). In preferred embodiments a seal or gasket (10) seals the valve cup (8) relative to the bead (6). The seal may be annular or disc shaped. It is preferably disc shaped. It may consist of materials known from the prior art which are suitable for using pharmaceutical formulations with fluorohydrocarbons as the propellants. Examples of suitable materials include thermoplasts, elastomers, materials such as neoprene, isobutylene, isoprene, butyl rubber, buna rubber, nitrile rubber, copolymers of ethylene and propylene, terpolymers of ethylene, propylene and a diene, e.g. butadiene, or fluorinated polymers. The preferred materials are ethylene/propylene/diene terpolymers (EPDM).

25 On the side of the valve cup (8) facing the inside of the container, a valve (9) is formed so that the valve stem (12) passes through the valve cup (8) to the other side. The valve (9) sits in the central opening of the gasket (10) to form a seal. The gasket (10)

and valve (9) together seal the valve cup (8) from the inside of the container, so that it cannot come into contact with the liquid in the container (2).

5 The valve (9) is constructed so that every element which is capable of coming into contact with the liquid inside the container (2) consists of a material which is corrosion-resistant with respect to this liquid. Such elements include for example the spring or springs (11), the valve stem (12), which projects from the inside to the outside through the opening (17) in the valve cup (8), the metering chamber (13) and the valve body (14). The spring (11) consists of steel, preferably a stainless steel. The
10 other elements of the valve (9) may consist, for example, of steel, the alloy described above and/or a plastic. The elements (12), (13) and (14) preferably consist of a plastic, particularly a polyester, most preferably polybutylene terephthalate.

As shown in Figure (1), one or more other gaskets or seals, e.g. the gaskets (15) and/or
15 (16), may be provided to prevent liquid or gas from escaping outwards from the inside of the container. The gasket or gaskets may be arranged so that the liquid inside the container comes into contact only with the container jacket and the valve, apart from the actual gasket or gaskets.

20 The gasket (15) seals off the valve stem, which is optionally vertically movable, at the point where it penetrates the valve cup (8). The gasket (16) seals the valve stem (12) inside the valve relative to the valve body (14) and/or the metering chamber (13). In this way, the gaskets (15) and (16) prevent any liquid or gas from escaping from the interior of the container along the outer casing of the valve stem and out of the canister
25 or from coming into contact with the valve cup by this route. The gaskets (15) and (16) may be made of the same material as the gasket (10), preferably an ethylene/propylene/diene terpolymer.

In one embodiment in which the valve cup (8) is not made of aluminium but of one of
30 the corrosion-resistant materials described above, it is not necessary for the gasket (10) together with the valve (9) to isolate the valve cup completely from the inside of the container. Therefore, it is not necessary in this case for the gasket (10) and valve (9)

to be in sealing contact with one another. There may be a gap between the gasket (10) and the valve (9). In such a case the gasket (10) sits directly on the underside of the valve cup (8), for example, and seals the edge of the valve cup (8) relative to the bead (6) on the container. The gasket (15) then seals the opening (17) in the valve cup (8)
5 from the interior of the container.

Figure 2 shows another embodiment of the valve cup (8) with embedded valve (9). This embodiment is largely identical to that in Figure 1. The major difference is that the gasket (10) and the gasket (16) in the embodiment in Figure 2 are combined to
10 form one gasket (18). The gasket (18) encloses the underside of the valve plate (18). It is arranged so that the valve body (14) is embedded in the gasket. The valve stem (12) passes through the gasket via the opening (19) which is located directly below the opening (17) in the valve cup (8). The opening (19) is of such dimensions as to seal the valve stem (12) relative to the valve cup (8). The sealing material for the gasket
15 (18) is identical to that described for the gasket (10).

The container (2) or canister consisting of container (2) and valve cup (8) with valve (9) according to the invention is particularly suitable for use with propellant gas formulations containing fluorohydrocarbons. Propellant gas formulations which can
20 preferably be used in conjunction with the invention are disclosed in WO 94/13262, to which reference is hereby made. Particularly preferred formulations disclosed therein are acid-stabilised and/or ethanol propellant gas formulations containing 1,1,1,2-tetrafluoroethane (TG 134a) and/or 1,1,1,2,3,3,3-heptafluoropropane (TG 227) as the propellant gas, particularly those which contain ipratropium bromide, oxitropium
25 bromide, albuterol, tiotropium bromide or fenoterol as active substance.

The container (2) or canister consisting of container (2) and valve cup (8) with valve (9) according to the invention is particularly suitable for use with propellant gas formulations containing fluorohydrocarbons. Propellant gas formulations which can
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tetrafluoroethane (TG 134a) and/or 1,1,1,2,3,3,3-heptafluoropropane (TG 227) as the propellant gas, particularly those which contain ipratropium bromide, oxitropium bromide, albuterol, tiotropium bromide or fenoterol as active substance.

- 5 Depending on the active substance, inorganic or organic acids may be used as stabilisers. Examples of inorganic acids include, in addition to halic acids and other mineral acids: sulphuric acid, hydrochloric acid, nitric acid or phosphoric acid, whilst examples of organic acids include ascorbic acid or citric acid. In the case of the salts of the active substances, the preferred acids are those wherein the anion is identical to
10 that of the salt of the active substance. Citric acid is generally suitable for all active substances and their salts and is also most preferred.

- The acid content is such that the pH of the formulation is between 1.0 and 7.0, preferably between 2.0 and 5.0 and most preferably at about 3.5. In the case of
15 inorganic acids the preferred acid content is in the range from about 0.00002 to 0.01 N. In the case of ascorbic acid the preferred content is roughly in the range from 0.0045 to 5.0 mg/ml and in the case of citric acid it is within the range from 0.0039 to 27.7 mg/ml.

- 20 The formulations may additionally contain ethanol as cosolvent. The preferred amount is 1.0 to 50.0% by weight of the formulation.

The following are some preferred formulations by way of example which can be stored in a canister or a container of the type described above:

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Example 1

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|---------------------------------|------------------------|
| Ipratropium bromide monohydrate | 0.001 - 2.5% by weight |
| Absolute ethanol | 0.001 - 50% by weight |
| TG 134a | 50.0 - 99.0% by weight |
| 30 Inorganic acid | 0.01 - 0.00002 normal |
| Water | 0.0 - 5.0% by weight |

Example 2

	Ipratropium bromide monohydrate	0.001 - 2.5% by weight
	Absolute ethanol	0.001 - 50% by weight
	TG 134a	50.0 - 99.0% by weight
5	Ascorbic acid	0.00015 - 5.0 mg/ml
	Purified water	0.0 - 5.0% by weight

Example 3

	Ipratropium bromide monohydrate	0.0187% by weight
10	Absolute ethanol	15.0000% by weight
	TG 134a	84.47730% by weight
	Citric acid	0.0040% by weight
	Purified water	0.5000% by weight
	Total	100.0000% by weight

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Example 4

	Ipratropium bromide monohydrate	0.0374% by weight
	Absolute ethanol	15.0000% by weight
	TG 134a	84.4586% by weight
20	Citric acid	0.0040% by weight
	Purified water	0.5000% by weight
	Total	100.0000% by weight

Example 5

25	Ipratropium bromide monohydrate	0.0748% by weight
	Absolute ethanol	15.0000% by weight
	TG 134a	84.4212% by weight
	Citric acid	0.0040% by weight
	Purified water	0.5000% by weight
30	Total	100.0000% by weight --

Example 6

	Fenoterol hydrobromide	0.192% by weight
	Absolute ethanol	30.000% by weight
	TG 134a	67.806% by weight
	Citric acid	0.002% by weight
5	Purified water	2.000% by weight
	Total	100.0000% by weight

A method of filling the canisters with the corresponding formulation might be, for example, the dual stage pressure fill method, the single stage cold fill method or the
10 single stage pressure fill method.